Advancing Prostate Cancer Treatment With T-Cell Engagers and Emerging Therapeutic Targets

AMGEN®
Oncology

Objectives

1. Discuss the unmet need in prostate cancer, with a focus on metastatic castration-resistant prostate cancer (mCRPC) where treatment options are limited
2. Review the role of immunotherapies, including the potential of T-cell engagers, in the treatment of prostate cancer
3. Provide an overview of PSMA, STEAP1, and DLL3 as emerging therapeutic targets in prostate cancer

DLL3, delta-like ligand 3; PSMA, prostate-specific membrane antigen; STEAP1, six-transmembrane epithelial antigen of prostate 1.

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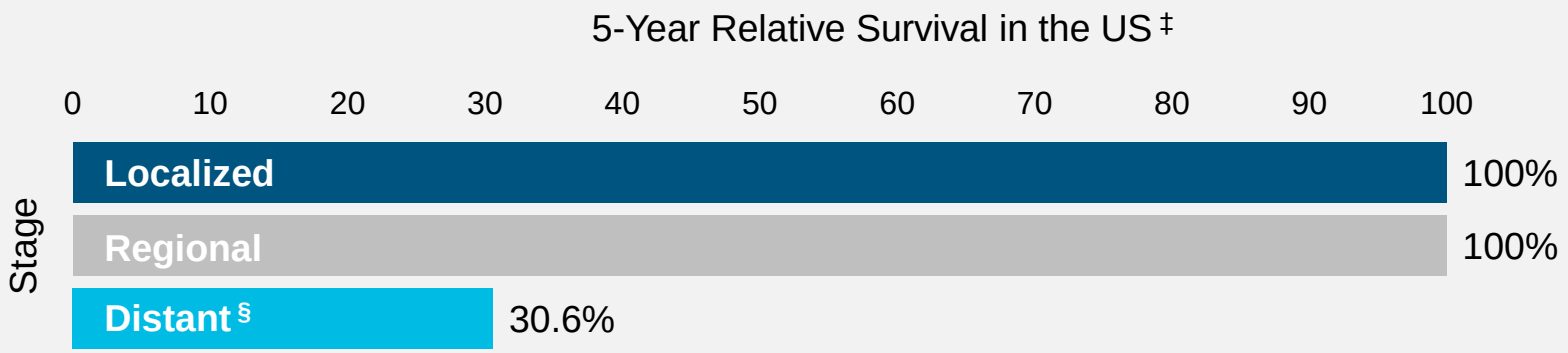
Prostate Cancer Is a Significant Cause of Cancer-Related Death in Men Worldwide [1]

~ 1.4 million new patients diagnosed and **375,000 estimated deaths** due to prostate cancer **worldwide** [1,*]

~ 250,000 new patients diagnosed and **34,100 estimated deaths** due to prostate cancer **in the US** [2,†]

Metastatic Prostate Cancer Is Associated With Reduced Survival, With Only ~ 1 in 3 Men Surviving Beyond 5 Years [3]



Of patients with metastatic prostate cancer who died within 5 years of diagnosis, prostate cancer was the cause of death in **~ 79% of patients** compared with other comorbidities [4,**]

*GLOBOCAN estimated cases and deaths in 2020. [1] †Estimated cases and deaths in the United States in 2021. [2] ‡Results from SEER 18 in male patients with prostate cancer from 2011–2017. [3]
§Cancer has metastasized. [3] **A retrospective study of 26,168 men with histologically proven metastatic prostate cancer diagnosed in the US from January 2000 to December 2016. [4]

1. Sung H, et al. *CA Cancer J Clin*. 2021;71:209-249. **2.** Siegel RL, et al. *CA Cancer J Clin*. 2021;71:7-33. **3.** National Cancer Institute. www.seer.cancer.gov. Accessed October 12, 2021.
4. Elmehrath AO, et al. *JAMA Netw Open*. 2021;4:e2119568.

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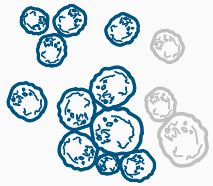
Most Patients With Prostate Cancer Progress to Advanced Disease [1]

Up to 20% of men advance to castration-resistant prostate cancer (CRPC) and no longer respond to hormonal therapy [2,3,*]



Of the men who advance to CRPC, **≥ 84% will have metastases** [2,†]

Progression to mCRPC Is Associated With Poor Outcomes [4]

Predicted survival rate is **~ 24 months** following progression to mCRPC [4]

Skeletal complications from bone metastases are increased (eg, bone pain and pathological fractures) [4]

Quality of life may be decreased (eg, bone pain, impairment in physical functioning, sleep disturbances) [5]

*When CRPC is defined in terms of a rise in PSA levels following castration. [2] †Sites of metastases typically include bone, lymph nodes, liver, and lung. [4]
mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

1. Ritch C, et al. *F1000Res.* 2018;7:1513. **2.** Kirby M, et al. *Int J Clin Pract*. 2011;65:1180-1192. **3.** Crawford ED, et al. *Urol Oncol*. 2017;35S:S1-S13. **4.** Frieling JS, et al. *Cancer Control*. 2015;22:109-120. **5.** Gater A, et al. *Health Qual Life Outcomes*. 2011;9:88.

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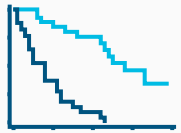
There Is an Unmet Need for Therapies That Can Improve Outcomes in mCRPC, Which Remains an Incurable and Difficult-to-Treat Disease

For ~ 20 years, the SOC treatment in mCRPC has been **taxanes** and **hormonal therapy** [1]



Despite improved outcomes with novel hormonal therapies (NHTs), **only 30%–78%** of patients with mCRPC may respond to these therapies [2,3,*]

mCRPC SOC treatment with taxanes and hormonal therapy slows disease growth but does not significantly shrink tumors and minimally reduces disease-related symptoms [1,4]

While NHTs have improved outcomes in some patients, mCRPC remains an incurable and difficult-to-treat disease because patients may develop resistance to these therapies [5,6]

Currently approved therapies only temporarily delay progression for the majority of men with mCRPC, highlighting the need for novel therapies, especially in later lines where treatment options are limited [1,5]

*Based on PSA response, defined as decline in PSA level of ≥ 50% from baseline. [2,3]

mCRPC, metastatic castration-resistant prostate cancer; NHT, novel hormonal therapy; PSA, prostate-specific antigen; SOC, standard-of-care.

1. Sartor O, et al. *N Engl J Med*. 2018;378:645-657. **2.** Fizazi K, et al. *Lancet Oncol*. 2012;13:983-992. **3.** Beer TM, et al. *N Engl J Med*. 2014;371:424-433. **4.** Sumanasuriya S, et al. *Cold Spring Harb Perspect Med*. 2018;8:a030635. **5.** Frieling JS, et al. *Cancer Control*. 2015;22:109-120. **6.** Crawford ED, et al. *Urol Oncol*. 2017;35S:S1-S13.

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Immunotherapy Utilizes the Patient's Own Immune System to Fight Cancer

Targeting tumor-associated antigens induces a **specific immune response** against antigen-expressing cancer cells vs nonspecific traditional therapies [1,2]

Stimulation of a **patient's own immune response** can result in a **long-term** response that **actively targets cancer cells** [3]

Immunotherapies May Offer Several Advantages in Treating Cancer

Disruption of inhibitory signaling pathways results in **restoration of the immune system** and **sustained anti-tumor activity**, overcoming limitations of traditional therapies with the potential to result in long-term survival [3,4]

Modulation of the tumor microenvironment to **enhance the engagement** of the immune system and cancer cells [5]

1. Fay EK, et al. *Cancers.* 2020;12:1752. **2.** Baudino TA. *Curr Drug Discov Technol.* 2015;12:3-20. **3.** Cha HR, et al. *Cancer Res.* 2020;80:1615-1623. **4.** Lim SM, et al. *Cancer Treat Rev.* 2021;99:102240. **5.** Murciano-Goroff YR, et al. *Cell Res.* 2020;30:507-519.

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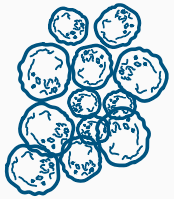
Barriers Remain for Immunotherapies in the Treatment of Prostate Cancer [1]

Despite recent advances with immunotherapies in various solid tumors, limited effect has been seen in prostate cancer [2]



Prostate cancers are often regarded as immunologically "**cold tumors**" with **minimal T-cell infiltration** [2]

Factors contributing to the cold prostate cancer tumor microenvironment (TME) include:

Abundance of immunosuppressive components, such as fibroblasts and regulatory T cells [3]

Low tumor mutational burden [4]

Loss of MHC Class I expression [4]

The cold TME resulting in minimal T-cell infiltration, along with the characteristically low tumor mutational burden, has led to the limited clinical responses seen with immunotherapies in prostate cancer [1]

MHC, major histocompatibility complex.

1. Cha HR, et al. *Cancer Res.* 2020;80:1615-1623. **2.** Bilusic M, et al. *Clin Cancer Res*. 2017;23:6764-6770. **3.** Stultz J, et al. *Prostate Cancer Prostatic Dis*. 2021;24:697-717. **4.** Vitkin N, et al. *Front Immunol*. 2019;10:603.

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Immunotherapy Options Remain Limited for Patients With Prostate Cancer [1]

Currently Approved Immunotherapies for Prostate Cancer Are Associated With Limitations

Limited adoption of therapy into clinical practice in part due to complex collection and administration process [2]

Significant proportions of patients are ineligible for therapy based on tumor testing [3,4]

Limited clinical benefit with therapies that target only a subset of patients with prostate cancer [5]

There is a need for novel immunotherapies that offer durable tumor responses and benefit a larger proportion of patients with prostate cancer

1. Bilusic M, et al. *Clin Cancer Res*. 2017;23:6764-6770. **2.** Sumanasuriya S, et al. *Cold Spring Harb Perspect Med*. 2018;8:a030635. **3.** FDA. www.fda.gov. Accessed October 11, 2021. **4.** Abida W, et al. *JAMA Oncol*. 2019;5:471-478. **5.** Stultz J, et al. *Prostate Cancer Prostatic Dis*. 2021;24:697-717.

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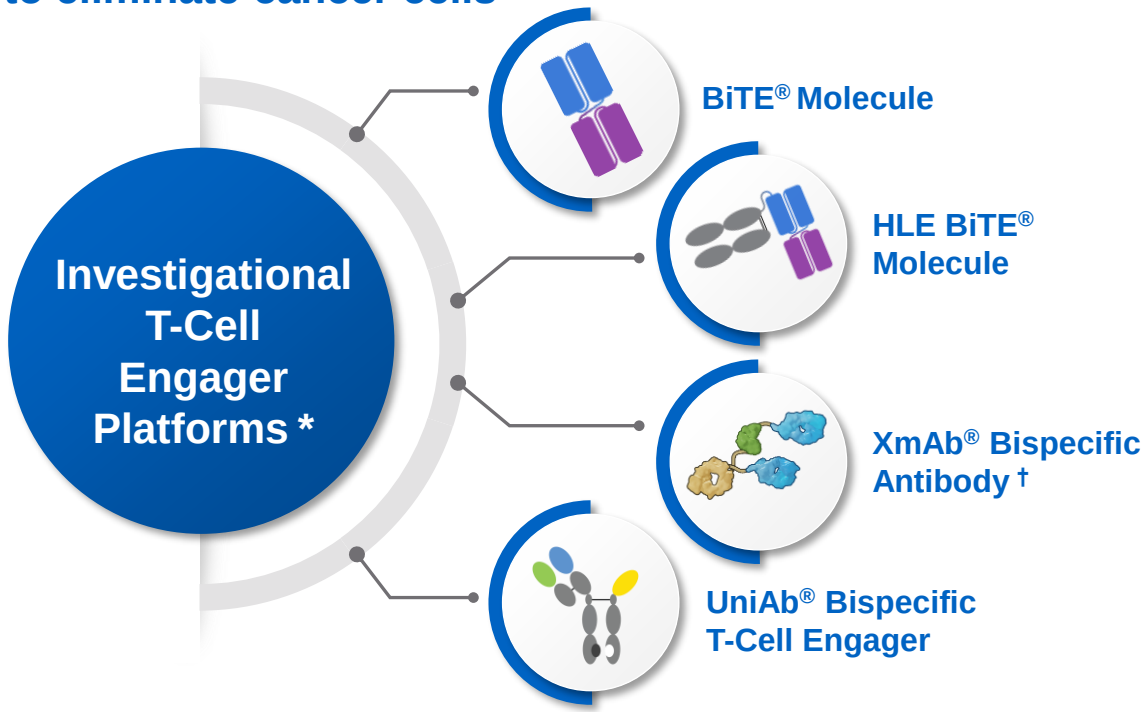
T-Cell Engagers Are Immunotherapies Being Investigated Across Cancer Types

T-cell engagers are a class of immunotherapy designed to engage a patient's own T cells to target a tumor-associated antigen to eliminate cancer cells [1-3]

T-cell engagers can be engineered for versatility to:

- Target various tumor-associated antigens [1]
- Enhance specificity by utilizing multiple domains that bind tumor-associated antigens [1]
- Extend half-life with the addition of an Fc domain [1]



Immunotherapies that directly engage a patient's own T cells to eliminate prostate cancer cells may help overcome the barriers of immunotherapies in the treatment of prostate cancer [4]

*Amgen is investigating a number of T-cell engaging platforms, including canonical and HLE BiTE® molecules, an XmAb® bispecific antibody, and a UniAb® bispecific T-cell engager. [5,6] †XmAb® is a registered trademark of Xencor, Inc. [5]

BiTE, Bispecific T-cell Engager; Fc, fragment crystallizable; HLE, half-life extended.

1. Lim SM, et al. *Cancer Treat Rev.* 2021;99:102240. **2.** Xencor. www.xencor.com. Accessed October 12, 2021. **3.** Teneobio. www.teneobio.com. Accessed October 12, 2021. **4.** Stultz J, et al. *Prostate Cancer Prostatic Dis*. 2021;24:697-717. **5.** Amgen pipeline. www.amgenpipeline.com. Accessed October 12, 2021. **6.** Cision PR Newswire. www.prnewswire.com. Accessed October 19, 2021.

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Antigens That Are Highly Expressed On Cancer Cells Are Compelling Therapeutic Targets for T-Cell Engagers [1-3]

Emerging Therapeutic Targets in Prostate Cancer

Prostate-Specific Membrane Antigen (PSMA)

Membrane protein that is highly expressed in prostate cancer [4]

Six-Transmembrane Epithelial Antigen of Prostate 1 (STEAP1)

Membrane protein that is highly expressed in prostate cancer [5]

Delta-Like Ligand 3 (DLL3)

Ligand that is upregulated on the surface of high-grade neuroendocrine tumors, including NEPC [6,7]

PSMA, STEAP1, and DLL3 represent promising therapeutic targets due to their high expression in prostate cancer

NEPC, neuroendocrine prostate cancer.

1. Yuraszeck T, et al. *Clin Pharmacol Ther*. 2017;101:634-645. **2.** Xencor. www.xencor.com. Accessed October 12, 2021. **3.** Teneobio. www.teneobio.com. Accessed October 12, 2021. **4.** Caromile LA, et al. *Sci Signal*. 2017;10:eaag3326. **5.** Gomes IM, et al. *Mol Cancer Res*. 2012;10:573-587. **6.** Puca L, et al. *Sci Transl Med*. 2019;11:eaav0891. **7.** Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561.

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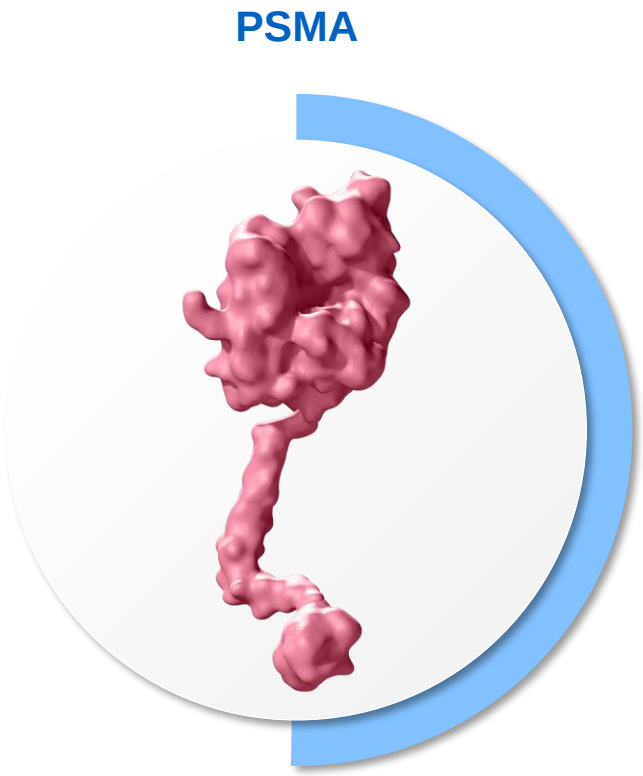
PSMA Is a Clinically Validated Therapeutic Target That Is Highly Expressed in Prostate Cancer Cells



- PSMA is a type II integral membrane protein that is expressed on the surface of prostate epithelial cells [1]
- PSMA is upregulated in most prostate tumors, with **> 85% of prostate cancer cells being PSMA-positive** [2,3]
- PSMA expression levels increase with disease progression and the transition to mCRPC [4,5]
- PSMA-based imaging may also aid in diagnosis, treatment assessment, and predict clinical outcomes in patients with mCRPC [6,7]
- PSMA is recognized as a clinically validated therapeutic target in prostate cancer and continues to be investigated in patients with mCRPC across clinical trials [8,9]

PSMA is a clinically validated therapeutic target due to its high expression in prostate cancer cells

mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

1. Caromile LA, et al. *Sci Signal*. 2017;10:eaag3326. **2.** Hupe MC, et al. *Front Oncol*. 2018;8:623. **3.** Minner S, et al. *Prostate*. 2011;71:281-288. **4.** Wright GL Jr, et al. *Urology*. 1996;48:326-334. **5.** Ross JS, et al. *Clin Cancer Res*. 2003;9:6357-6362. **6.** Liu C, et al. *Cancer Med*. 2020;9:3278-3286. **7.** Hofman M. *Clin Adv Hematol Oncol*. 2019;17:370-373. **8.** Sartor O, et al. *N Engl J Med*. 2021;385:1091-1103. **9.** Tran B, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. Abstract 609O.

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STEAP1 Is a Potential Therapeutic Target That Is Highly Expressed in Prostate Cancer

STEAP1

- STEAP1 is localized in the plasma membrane of epithelial cells located at cell to cell junctions and is primarily expressed in prostate tissue [1]
- STEAP1 expression is low or absent in normal tissues, and its expression is increased in several types of human cancers, including prostate cancer [2]
- STEAP1 is induced by the androgen receptor and is **overexpressed in > 80% of prostate cancers**, including bone and lymph node metastases [2-4]

The overexpression of STEAP1 in prostate cancer highlights its potential as a therapeutic target

STEAP1, six-transmembrane epithelial antigen of prostate 1.

1. Gomes IM, et al. *Mol Cancer Res*. 2012;10:573-587. **2.** Barroca-Ferreira J, et al. *Curr Cancer Drug Targets*. 2018;18:222-230. **3.** Ihlaseh-Catalano SM, et al. *Histopathology*. 2013;63:678-685.
4. Nolan-Stevaux O. Presented at: American Association for Cancer Research Virtual Annual Meeting I; April 27–28, 2020. Abstract DDT02-04.

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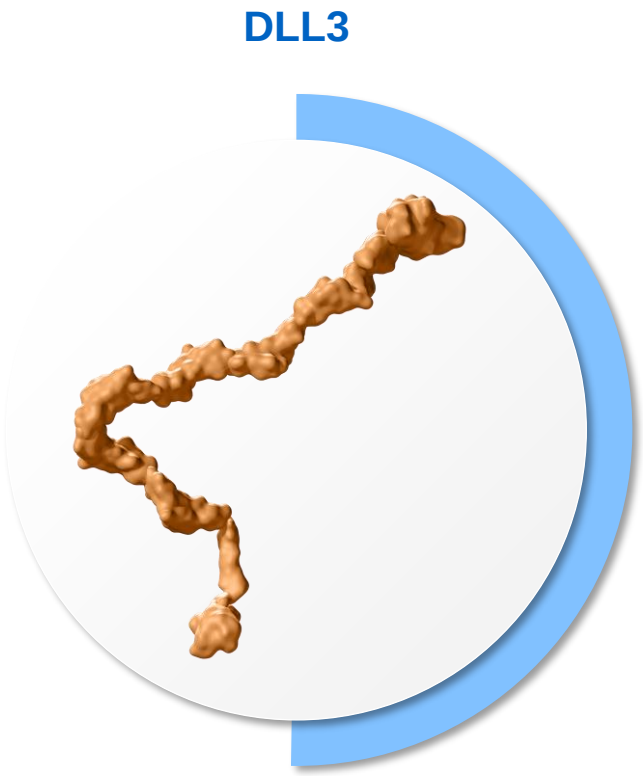
DLL3 Is an Attractive Therapeutic Target That Is Highly Expressed in Neuroendocrine Prostate Cancer (NEPC)



- DLL3 is an inhibitory Notch ligand [1]
- DLL3 is upregulated on the surface of SCLC and high-grade neuroendocrine tumors, including NEPC [1,2]
  - In a study of 423 patients with prostate cancer (735 samples), **DLL3 was expressed in most NEPC samples (77%), with 64% of cancer cells expressing DLL3** [1]

The upregulation of DLL3 on NEPC tumors identifies DLL3 as a compelling therapeutic target

DLL3, delta-like ligand 3; SCLC, small cell lung cancer.

1. Puca L, et al. *Sci Transl Med*. 2019;11:eaav0981. **2.** Sabari JK, et al. *Nat Rev Clin Oncol*. 2017;14:549-561.

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Amgen Is Committed to Developing Novel Targeted Immunotherapies to Address the Needs of Patients With Prostate Cancer

Amgen is focused on addressing the **needs of patients with mCRPC**, a disease that significantly impacts QoL and has limited treatment options [1-5]

Amgen is on the **leading edge of immunotherapy development in prostate cancer**, employing innovative trial design and advanced imaging technology with an aspiration to transform the lives of men with prostate cancer [3-6]

Amgen is investigating various modalities **designed to engage the patient's own immune system** to target tumor-associated antigens and mediate killing of prostate cancer cells [6]

Amgen is investigating various modalities and targets, with the goal of developing therapies capable of driving durable tumor responses in patients with prostate cancer [3-7]

mCRPC, metastatic castration-resistant prostate cancer; QOL, quality of life.

1. Frieling JS, et al. *Cancer Control*. 2015;22:109-120. **2.** Gater A, et al. *Health Qual Life Outcomes*. 2011;9:88. **3.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03792841. Accessed October 12, 2021. **4.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04631601. Accessed October 12, 2021. **5.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04221542. Accessed October 12, 2021. **6.** Amgen pipeline. www.amgenpipeline.com. Accessed October 12, 2021. **7.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04702737. Accessed October 12, 2021.

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Summary

Prostate cancer is a significant cause of cancer-related death in men worldwide [1]

Despite recent advances in various solid tumors, currently approved immunotherapies only target a subset of patients with prostate cancer and provide limited clinical benefit [2]

T-cell engagers represent a class of immunotherapies designed to engage a patient's own immune system to eliminate cancer cells [3,4]

PSMA, STEAP1, and DLL3 are highly expressed in prostate cancer, highlighting their potential as promising targets for the treatment of prostate cancer [5-7]

DLL3, delta-like ligand 3; PSMA, prostate-specific membrane antigen; STEAP1, six-transmembrane epithelial antigen of prostate 1.

1. Sung H, et al. *CA Cancer J Clin*. 2021;71:209-249. **2.** Stultz J, et al. *Prostate Cancer Prostatic Dis*. 2021;24:697-717. **3.** Lim SM, et al. *Cancer Treat Rev*. 2021;99:102240. **4.** Xencor. www.xencor.com. Accessed October 12, 2021. **5.** Caromile LA, et al. *Sci Signal*. 2017;10:eaag3326. **6.** Gomes IM, et al. *Mol Cancer Res*. 2012;10:573-587. **7.** Puca L, et al. *Sci Transl Med*. 2019;11:eaav0891.

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